No. 210

THE ALKALOIDS OF IPECACUANHA
PART IV.

BY

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CXLIV.—*The Alkaloids of Ipecacuanha. Part IV.*

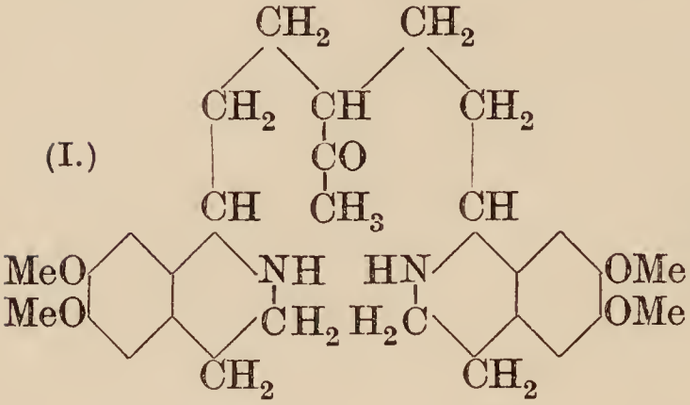
By William Harrison Brindley and Frank Lee Pyman.

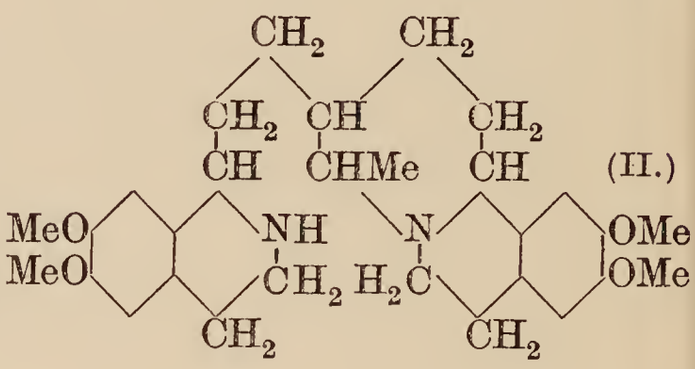
In the earlier parts of this series (Carr and Pyman, J., 1914, **105**, 1591; Pyman, Part II, J., 1917, **111**, 419; Pyman, Part III, J., 1918, **113**, 222), the formula $C_{29}H_{40}O_4N_2$ was established for emetine, and Hesse's observation (*Pharm. J.*, 1898, **7**, 98) that it contains four methoxyl groups, and Keller's discovery (*Arch. Pharm.*, 1911, **249**, 512) that it is a secondary-tertiary base, were confirmed. The relations of emetine to its subsidiary alkaloids were determined, and many reactions of these bases were described. It was shown that emetine is a derivative of *iso*quinoline, since it gave 6 : 7-dimethoxy*iso*quinoline-1-carboxylic acid on oxidation.

Some two years ago, Professor Robert Robinson, F.R.S., suggested, on the basis of a theory of structural or genetic relationships of alkaloids of the *iso*quinoline group, that emetine and its congeners might be derived from two molecules of dihydroxyphenylalanine, two molecules of glyceraldehyde, and one molecule of dihydroxy-

acetone by processes of condensation, decarboxylation, methylation, and reduction. Coming closer to normal laboratory syntheses in order to simplify the discussion, one might imagine the condensation of two molecules of acraldehyde and one molecule of acetone to the ketone-dialdehyde,* $(CHO\cdot CH_2\cdot CH_2)_2CH\cdot CO\cdot CH_3$, and the subsequent condensation of this intermediate with β-(3 : 4-dimethoxyphenyl)ethylamine to the *iso*quinoline derivative (I).

(I.)





(II.)

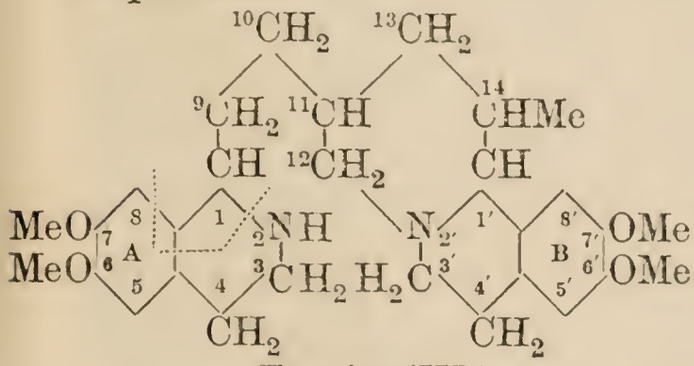
On reduction and dehydration, (II) is obtained, and this, it was thought, might be the constitution of emetine. Recently, this field of work has been entered by Späth and Leithe (*Ber.*, 1927, **60**, 688), who have put forward a partial formula for emetine in harmony with the above formula (II), in that it contains two dimethoxy-*iso*quinoline residues connected through the 1-position in each case. It has consequently become necessary to publish Robinson's formula at once. Whilst this formula is able to afford an explanation of most of the salient facts in the chemistry of the alkaloids related to emetine, there is undoubtedly a difficulty in connexion with the nature of rubremetine.

Oxidation of emetine with ferric chloride, bromine, or iodine, or of *O*-methylpsychotrine with bromine or iodine, yields the deep red rubremetine salts, *e.g.*, rubremetinium chloride, $C_{29}H_{33}O_4N_2Cl$, in which one of the nitrogen atoms has lost its basicity and the other has become quaternary (Carr and Pyman; Pyman, Part II, *loc. cit.*; Karrer, *Ber.*, 1916, **49**, 2057).

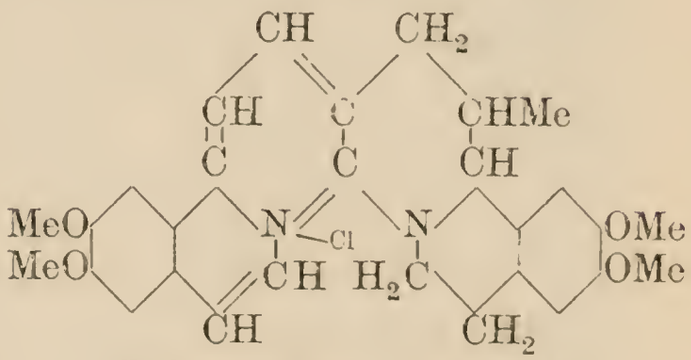
It would appear, therefore, that the removal of eight hydrogen atoms from emetine in the process of oxidation to rubremetine should be accompanied by some structural change which could destroy the salt-forming power of one of the nitrogen atoms. This would hardly be the case with rubremetine formulæ derived from (II) by simple oxidation of two of the three hydrogenated pyridine rings, and in this respect Robinson's formula for emetine seems to us unsatisfactory. It has led us, however, to put forward a formula

* The type $R_2CH\cdot CO\cdot CH_3$ was preferred to $R\cdot CH_2\cdot CO\cdot CH_2R$ because cuskhygrine is a representative of the former class.

for emetine (III), differing from Robinson's only in the position of the *C*-methyl group, which affords a convincing explanation of the formation of rubremetine (IV), and is equally satisfactory in other respects.



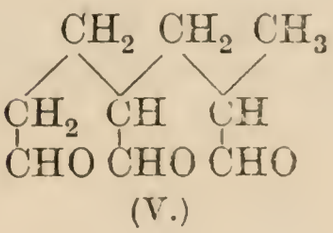
Emetine (III.)



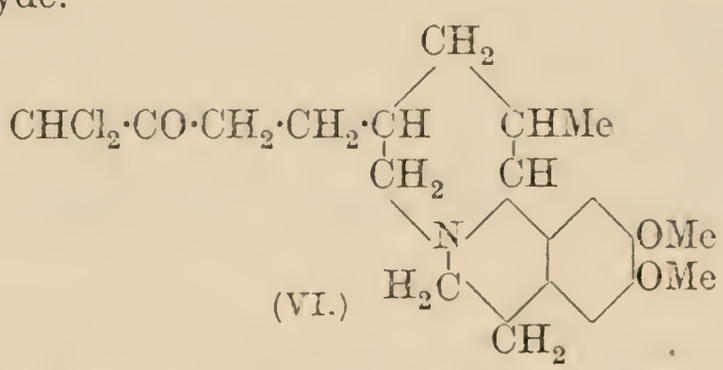
Rubremetinium chloride (IV.)

The loss of basicity of one of the nitrogen atoms in the conversion of emetine into rubremetine is thus attributed to amidine formation, a double bond connecting N(2) with C(12). Evidence is given below that *O*-methylpsychotrine, and therefore probably rubremetine also, contains a double bond between C(1) and C(9), and this necessitates a third double bond between C(10) and C(11) to complete the unsaturation of the new ring. The fourth double bond is assumed to lie between C(3) and C(4), thus giving the berberine-like structure for rubremetine shown above. This formula accords with the facts that rubremetine cannot be converted into derivatives analogous to oxyberberine or berberine-acetone. It is also in harmony with the fact that no substance analogous to rubremetine can be made by the oxidation of *N*-methylemetine with bromine.

Turning to the new formula for emetine (III) itself, it may be pointed out that the skeleton of this formula might be produced phytochemically by the condensation of two molecules of dihydroxyphenylalanine with a condensation product (V) derived from three molecules of glyceraldehyde.



(V.)



(VI.)

This process leads to two alternative formulæ for emetine, namely, (III), and a second formula in which the *C*-methyl group is attached to C(9) instead of C(14), but formula (III) is preferred for reasons given later. It may be pointed out, however, that in both formulæ this methyl group is shown in a position relative to an *iso*quinoline

ring, which it is known to occupy in other alkaloids, for example, corydaline.

The new formula for emetine permits the deduction of intelligible formulæ for the subsidiary alkaloids of ipecacuanha.

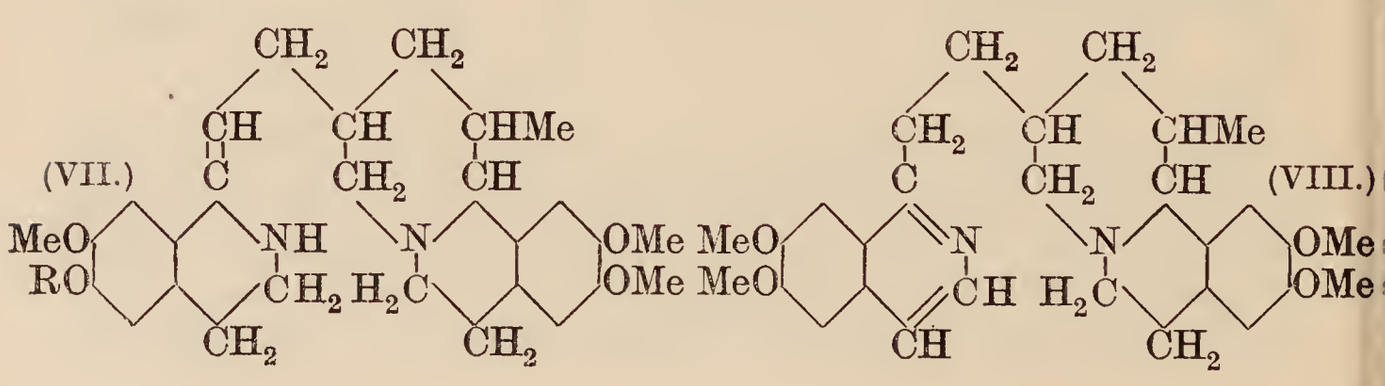
Cephæline, $C_{28}H_{38}O_4N_2$, contains a phenolic hydroxyl group in the place of one of the methoxy-groups of emetine, and yields emetine on methylation. It yields on oxidation with ferric chloride a base, $C_{20}H_{27}O_3NCl_2$, from which no nitrosoamine could be prepared, containing two methoxy-groups, and two chlorine atoms which were readily replaceable by hydroxyl (Carr and Pyman, *loc. cit.*), giving a compound $C_{20}H_{29}O_5N$, which appeared to have amphoteric character. The base $C_{20}H_{27}O_3NCl_2$ contains only one benzene nucleus (Dobbie and Fox, J., 1914, **105**, 1639), whence it follows that the benzene nucleus containing the phenolic hydroxyl group has been eliminated, together with one of the nitrogen atoms. The only explanation of the formation of the base $C_{20}H_{27}O_3NCl_2$ which seems to us plausible is indicated by dotted lines in the emetine formula (III), and leads to the conclusion that the phenolic hydroxyl group of cephæline must be placed in ring A, probably in position 6 of the *iso*quinoline ring. The choice of position 6 for this hydroxyl group is confirmed by evidence discussed below in connexion with psychotrine.

The properties of the base $C_{20}H_{27}O_3NCl_2$ are expressed by the formula (VI). Its conversion into the substance $C_{20}H_{29}O_5N$ by means of cold aqueous sodium hydroxide may be attributed to the formation of a substituted glyoxal, which then undergoes a change resembling the transformation of methylglyoxal into lactic acid. The substance $C_{20}H_{29}O_5N$ thus has the formula (VI) with

$$\cdot CH(OH)\cdot CO_2H$$

in place of $\cdot CO\cdot CHCl_2$.

Psychotrine, $C_{28}H_{36}O_4N_2$ (VII, R = H), yields on reduction cephæline and a stereoisomeride *iso*cephæline. *O*-Methylpsychotrine, $C_{29}H_{38}O_4N_2$ (VII, R = Me), yields on reduction emetine and *iso*emetine. They, therefore, contain a double linking, and saturation of this renders (at least) one additional carbon atom asymmetric (Carr and Pyman; Pyman, Parts II and III, *locc. cit.*) :



This condition can be fulfilled in many ways, but it is shown below that *O*-methylpsychotrine gives a good yield of psychotrine on partial hydrolysis with one molecule of acid. One of the four methoxy-groups is thus preferentially hydrolysed, and it must be in ring A, since cephæline, and therefore psychotrine, contains hydroxyl in this ring. It is suggested that the cause of the preferential hydrolysis is the presence of a double bond between C(1) and C(9), and that the methoxy-group in the para-position to the substituted vinyl group has become hydrolysed.

Confirmation of the situation of the double linking in the αβ-position to a benzene nucleus is afforded by the fact that *O*-methylpsychotrine yields on reduction, besides emetine and *iso*emetine, a demethoxyemetine or demethoxy*iso*emetine (base C, Part II, *loc. cit.*) in which one of the methoxy-groups has been replaced by hydrogen, for there is evidence (Semmler, *Ber.*, 1908, **41**, 2556; Salway, J., 1910, **97**, 2413) that a substituted vinyl group facilitates the replacement by hydrogen of alkyloxy-groups situated in the para-position with respect to it. The deep yellow colour of psychotrine base is also in accord with formula (VII).

The reason why formula (III) for emetine is preferred to that in which the *C*-methyl group is attached to C(9) is that *O*-methylpsychotrine gives emetine and *iso*emetine in fair yield on reduction, in spite of the complications introduced by demethoxylation, and it is therefore considered probable that only one additional carbon atom is rendered asymmetric by the reduction, giving two isomerides, whereas the alternative formula requires the rendering of two additional carbon atoms asymmetric, thus giving four possible isomerides.

Emetamine, $C_{29}H_{36}O_4N_2$ (VIII), is a ditertiary base yielding on reduction a mixture from which a small quantity of *iso*emetine can be isolated as benzoyl derivative. Emetamine is more feebly basic than *O*-methylpsychotrine (Pyman, Part II, *loc. cit.*), and may be regarded as containing the *iso*quinoline ring A in the unsaturated condition. Formula (VIII) accords with the facts that (1) although emetamine contains two atoms of hydrogen fewer than *O*-methylpsychotrine, it is not formed in the incomplete oxidation of *O*-methylpsychotrine to rubremetine, and (2) it cannot be converted into rubremetine.

The purity of the preparation of emetamine described in Part II has now been confirmed by the fractionation of a considerable quantity of this base, which has been characterised further by the preparation of a number of salts.

Experimental.

O-*Methylpsychotrine* has now been crystallised. It separates from hot dry ether in well-formed prisms, m. p. 123—124° (corr.) (Found : C, 73·0; H, 8·3. $C_{29}H_{38}O_4N_2$ requires C, 72·7; H, 7·9%). It is sparingly soluble in hot dry ether, almost insoluble in cold dry ether, but readily soluble in cold alcohol. In commercial absolute alcohol it had $[\alpha]_D$ + 43·2° (c = 1); $[\alpha]_D$ + 43·4° (c = 2·1); $[\alpha]_D$ + 43·2° (c = 3·9).

O-*Methylpsychotrine picrate* crystallises from acetone in octagonal plates which, after being dried at 100°, soften from 142° and gradually melt up to 175° (corr.).

Oxidation of O-*Methylpsychotrine.*—(1) *By permanganate.* The base from 6 g. of methylpsychotrine hydrogen oxalate in acetone (150 c.c.) was oxidised by the addition of a saturated aqueous solution of potassium permanganate (35 g.) in the course of ½ hour with thorough stirring, the temperature of the solution rising from 16° to 24°. After the products had been worked up as described in the oxidation of emetine by permanganate (Carr and Pyman, *loc. cit.*, p. 1630), the only crystalline product obtained was 6 : 7-dimethoxy*iso*quinoline-1-carboxylic acid (yield 0·16 g.), which was recognised by its appearance, content of water of crystallisation (Found : loss at 100°, 13·9. Calc., 13·4%), and behaviour on heating, the dried substance melting from 204° to 209° (corr.) according to the rate of heating, effervescing, and leaving an alkaline residue.

(2) *By chromic acid.* On adding aqueous chromic acid in excess to a warm aqueous solution of *O*-methylpsychotrine sulphate, a brown, gummy precipitate was obtained which became a bright yellow, crystalline powder on rubbing (Found, in substance dried at 100° : Cr, 13·9. $C_{29}H_{38}O_4N_2,H_2Cr_2O_7$ requires Cr, 14·9%). It was almost insoluble in water. This salt (1·6 g.) was suspended in water at 100° for 60 hours, the volume being kept at 60—70 c.c. The product was mixed with sodium hydroxide, extracted with ether (E), and filtered. The filtrate was acidified with hydrochloric acid, and extracted with chloroform, which left 0·25 g. of residue on distillation. A hot aqueous extract of this residue deposited rubremetine hydrochloride, recognised by its characteristic appearance and m. p. (air-dried, 125°; dried at 100°, from 160°). The ethereal extract (E) gave crude *O*-methylpsychotrine (0·45 g.), yielding 0·35 g. of the crystalline hydrogen oxalate from which the pure base (m. p. 123—124°) was readily obtained.

Partial Demethylation of O-*Methylpsychotrine.*—Methylpsychotrine sulphate heptahydrate (10 g.) and hydrochloric acid (1·54 c.c.; 34%) were heated for 6 hours at 170°. The product was dissolved

in water (50 c.c.) and shaken with ether, and excess of ammonia was added gradually; psychotrine (3·0 g.) then crystallised. This was dissolved in alcohol and mixed with an alcoholic solution of oxalic acid (1·5 g.); psychotrine hydrogen oxalate (3·2 g.) then separated (mother-liquor M). The filtrate from the psychotrine was separated into ethereal and aqueous layers and the former was extracted with aqueous sodium hydroxide (ethereal solution E). This was mixed with excess of ammonium chloride, combined with the aqueous layer and extracted with chloroform; the extract then gave with alcoholic oxalic acid more psychotrine hydrogen oxalate (2·1 g.). The mother-liquor from this and the mother-liquor M gave, after further similar treatment, another small crop (0·25 g.) of the same salt. The residue from the ethereal solution E gave, with alcoholic oxalic acid, methylpsychotrine hydrogen oxalate (2·4 g.).

The yields in this experiment and others in which the period and temperature of heating were varied appear below:

Time (hrs.).	Temp.	% Yield of psychotrine.	% Methylpsychotrine recovered.
3	150°	8	74
6	150	12	71
3	170	37	50
6	170	54	23

The psychotrine obtained by demethylation of methylpsychotrine was identical with the natural alkaloid. The bases from each source and mixtures of the two sintered from 115° and melted and effervesced at 122° (corr.), when air-dried, and softened from 122° and melted and effervesced at about 129° (corr.), after drying in a vacuum over sulphuric acid. Psychotrine from its methyl ether, like the natural base, crystallised from aqueous acetone in well-formed, yellow prisms containing $4H_2O$ (Found: H_2O, 13·3. Calc.: H_2O, 13·4%). Crystals from each source were found to be identical crystallographically by Mr. G. Greenwood, M.Sc., of the University of Manchester, to whom the authors are much indebted for his examination and for the following data:

Crystal system: orthorhombic. $a : b : c = 0{\cdot}989 : 1 : 1{\cdot}209$.
Forms observed: {100} {010} {110} + {101}.

Angle measured.	Natural psychotrine (obs.).	Psychotrine from its methyl ether (obs.).	Calc.
(100) : (101)	39° 20′	39° 18′	—
(110) : (101)	56° 35′	56° 41′	—
(100) : (110)	44° 38′	44° 50′	44° 41′

Mr. Greenwood adds: "It is interesting that the ratio $a : b$ is so near to 1 : 1 and the angle (100) : (110) to 45°. If this were actually the case, the crystal would be tetragonal. I am afraid the

angle measurements were really not good enough to settle this point. Also the crystals were too poor to examine the optical properties, which would again have decided this question. However, judging from the geometrical properties of the faces on the ends of the crystals, I think that there is no doubt that the crystals are not tetragonal and that the equality of *a* and *b* is merely a chance effect."

Psychotrine hydrogen oxalate readily separates in nearly colourless needles when alcoholic solutions of its constituents are mixed. It is very sparingly soluble in alcohol, but readily soluble in water. After drying in a vacuum over sulphuric acid, it softens from 130° and melts and effervesces up to 145° (corr.) [Found, (*a*) in salt crystallised from water, (*b*) in salt from alcohol : loss in vacuum over H_2SO_4, (*a*) 10·3; (*b*) 9·0. $C_{28}H_{36}O_4N_2,2C_2H_2O_4,4\frac{1}{2}H_2O$ requires loss of $4H_2O$, 10·0%. Found in dried salt : C, 58·7, 58·6; H, 6·6, 6·6. $C_{28}H_{36}O_4N_2,2C_2H_2O_4,\frac{1}{2}H_2O$ requires C, 58·8; H, 6·3%].

Emetamine.

Purification of Emetamine.—111 G. of emetamine hydrogen oxalate having $[\alpha]_D - 5°$, prepared by the method described earlier (Pyman, Part II, *loc. cit.*), were subjected to further fractionation as follows. The base was regenerated in chloroform by means of sodium hydroxide, and extracted six times with sufficient 2% sulphuric acid to remove 5% of the base at each extraction. Each extract and the mother-liquor were then basified, and the extracted bases were converted separately into the hydrogen oxalates. The yields and specific rotatory powers (of air-dried salt in water; $c = 4$) were as follows : (1) 4·6 g. (coloured); (2) 5·2 g., $[\alpha]_D - 4·7°$; (3) 5·0 g., $[\alpha]_D - 5·7°$; (4) 4·6 g., $[\alpha]_D - 6·2°$; (5) 5·0 g., $[\alpha]_D - 6·0°$; (6) 5·2 g., $[\alpha]_D - 6·4°$; remainder 55·7 g., $[\alpha]_D - 6·3°$. The last fraction, which was regarded as pure, was converted into the base, and through this into other salts. Its specific rotatory power is in close agreement with that previously recorded ($[\alpha]_D - 6·0°$).

Emetamine.—When emetamine is regenerated, in chloroform, from a salt and crystallised from ethyl acetate, it is free from solvent and melts at 153—154° (corr.) [Pyman, *loc. cit.*, gives 155—156° (corr.)], but when it is regenerated in ether, the ethereal solution, after being dried for a few minutes over potassium carbonate and filtered, deposits emetamine in colourless needles containing solvent of crystallisation. In this form, the air-dried base has m. p. 138—139° (corr.), and $[\alpha]_D + 13·6°$ in commercial absolute alcohol ($c = 2·2$); after drying in a vacuum at 100°, the base has m. p. 142—143° (corr.). It appears to contain $\frac{1}{2}$ mol. of ether of crystallisation [Found, in air-dried base : loss at 100° in a vacuum, 7·1; loss over

H_2SO_4, 6·9; C, 71·6, 71·6, 71·7; H, 7·3, 7·4, 7·9. $C_{29}H_{36}O_4N_2,\frac{1}{2}Et_2O$ requires loss of $\frac{1}{2}Et_2O$, 7·2; C, 72·4; H, 8·0%. Found, in dried base: *M* (in camphor), 447. $C_{29}H_{36}O_4N_2$ requires *M*, 476]. Emetamine of m. p. 153—154° can be converted into the lower-melting form by preparing a salt and regenerating the base in ether, but not by simple crystallisation from ether. On the other hand, emetamine of m. p. 138—139° yields the base of m. p. 153—154° on drying and crystallisation from ethyl acetate after seeding with the variety of higher m. p.

Emetamine hydrogen oxalate prepared from the pure base contained $3H_2O$, had $[\alpha]_D$ — 6·1° in aqueous solution ($c = 4·4$), and effervesced at 172° (corr.), these figures being in close agreement with those previously found for this salt (Pyman, *loc. cit.*).

Emetamine hydrochloride crystallises from concentrated hydrochloric acid in colourless, glistening needles; these, if air-dried, melt at 77—80°, but after being dried in a vacuum over sulphuric acid, the salt softens and effervesces at 218—223° (corr.) (Found, in air-dried salt: loss in a vacuum over H_2SO_4, 21·9; loss at 100°, 21·9. $C_{29}H_{36}O_4N_2,2HCl,8\frac{1}{2}H_2O$ requires H_2O, 21·8%. Found, in dried salt: Cl, 12·5. $C_{29}H_{36}O_4N_2,2HCl$ requires Cl, 12·9%). The hydrated salt had $[\alpha]_D$ — 17·5° in aqueous solution ($c = 4·1$). It is very readily soluble in cold water.

Emetamine hydriodide is deposited as an oil on adding sodium iodide to an aqueous solution of the hydrochloride. A solution of the oil in methyl alcohol, on spontaneous evaporation, deposits the salt in a microcrystalline form which (dried at 100°) softens from 208° and effervesces up to 274°.

Emetamine nitrate is precipitated in rosettes of acicular prisms on the addition of dilute nitric acid to an aqueous solution of the hydrochloride. After crystallisation from water, it forms prismatic needles.

The air-dried salt has m. p. 165—166° (corr.), and $[\alpha]_D$ — 7·3° in aqueous solution ($c = 2·6$) (Found, in air-dried salt: loss in a vacuum over H_2SO_4, 5·8. $C_{29}H_{36}O_4N_2,2HNO_3,2H_2O$ requires H_2O, 5·6%. Found, in dried salt: C, 58·0; H, 6·3. $C_{29}H_{36}O_4N_2,2HNO_3$ requires C, 57·8; H, 6·3%). On heating this salt at 100° either in the dry state or in strong aqueous solution, decomposition takes place.

Emetamine picrate is precipitated on mixing hot alcoholic solutions of the base (1 mol.) and picric acid (2 mols.), and after crystallisation from acetone forms long, yellow needles, which, after drying at 100°, begin to soften at 147° and gradually melt and effervesce up to 173° (corr.). It is very sparingly soluble in hot water, hot alcohol, or cold acetone.

Attempts to prepare emetamine acetate, salicylate, sulphate, and tartrate in crystalline form were unsuccessful.

Emetamine dimethiodide was prepared by heating the base with methyl iodide for 7 hours at 100°. It crystallised from aqueous alcohol in prismatic needles, which began to effervesce at 238° (corr.) (Found, in air-dried salt : loss at 110°, 2·2. $C_{31}H_{42}O_4N_2I_2,H_2O$ requires H_2O, 2·3%. Found, in dried salt : I, 33·0. $C_{31}H_{42}O_4N_2I_2$ requires I, 33·4%).

Action of Bromine upon Emetamine.—The base from emetamine hydrogen oxalate (1·8 g.) in chloroform (30 c.c.) was mixed with bromine (0·25 c.c.) in chloroform (10 c.c.). After 5 minutes, the solution was shaken with ammonia and dried with potassium carbonate, and the solvent was removed. The residue was extracted with boiling water, and the extract concentrated; it then deposited less than 0·1 g. of a red, microcrystalline substance, resembling rubremetine hydrobromide in colour and sparing solubility in water, but melting, when air-dried, at 185—190°. (Air-dried rubremetine hydrobromide melts at about 115—120°.) The material insoluble in hot water was dissolved in dilute hydrochloric acid, and the bases were liberated by ammonia in the presence of ether, a considerable amount of dark brown resinous material being precipitated; the ethereal solution gave a residue (0·3 g.), from which emetamine hydrogen oxalate (0·25 g.; m. p. 165—170°) was prepared.

Reduction of Emetamine.—(a) *With sodium and alcohol.* In view of the importance attaching to the formation of benzoyl*iso*emetine from emetamine (Part II, p. 443), the reduction of emetamine with sodium and alcohol was repeated, the specially purified emetamine described above being used, and the formation of *iso*emetine was confirmed by the isolation of its benzoyl derivative.

(b) *With tin and hydrochloric acid.* The reduction of emetamine by this means proceeds very slowly, and in the following experiment much emetamine was recovered unchanged, but again benzoyl-*iso*emetine was readily obtained from the reduced portion.

The base regenerated from emetamine hydrogen oxalate (3·55 g.) was heated with alcohol (20 c.c.), concentrated hydrochloric acid (20 c.c.), and tinfoil (8 g.) for 13 hours under reflux. The base (1·3 g.), regenerated in ether, was converted into hydrogen oxalate in alcohol; crude emetamine hydrogen oxalate (1·1 g.) then crystallised. The base (0·4 g.) regenerated from the mother-liquor was mixed with benzoic anhydride (0·4 g.) in dry ether; the deposited benzoyl*iso*emetine (0·08 g.), after being washed with acetone, melted at 207° (corr.), alone or mixed with a known specimen of benzoyl*iso*emetine.

The authors desire to thank Professor Robert Robinson, F.R.S., for the very considerable help which he has given them by suggestion and discussion in determining the constitution of the alkaloids of ipecacuanha, and to thank Mr. J. A. Goodson, F.I.C., for assistance in the earlier stages of the separation of emetamine from *O*-methylpsychotrine.

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